PATENT SPECIFICATION

NO DRAWINGS

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COMPLETE SPECIFICATION

Improvements in or relating to Freeze-Dried Medicaments

We, THE UPJOHN COMPANY, a corporation organized and existing under the laws of the State of Delaware, United States of America, of 301 Henrietta Street, Kalamazoo, State of Michigan, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to freeze-dried parenteral products and the method for preparation thereof. More particularly, this invention relates to parenteral compositions comprising mannitol as the freeze-dried cake both alone and in combination with a parenterally administrable medicinal agent.

Freeze-drying has been used to protect medicinal compositions and other materials, such as food products, against thermal decomposition or oxidation and to protect the potency of such compositions or other materials. Freeze-drying is used in particular to remove water or other solvents from such products as vitamins and antibiotics, to give dried products having prolonged stability. Freeze-drying is usually carried out by freezing a solution of the material to be dried and removing the water or solvent by sublimation while the material to be dried remains in the solid state. The removal of the water or solvent leaves a lyophilic porous residue, hereinafter called the cake, which usually readily redissolves in the water or other solvent to be used for administering the produce to a patient. Freeze-drying has the advantage, compared with drying by ordinary distillation, in that the low temperature reduces or prevents decomposition or the loss of volatile substances, the product is highly porous and thus generally more readily soluble in water or solvents than the ordinarily dried product and coagulation is minimized.

Prior to the present invention, however, mannitol was not used in the formulation of freeze-dried products, and such products as were known, not containing mannitol presented certain disadvantages. Such disadvantages were noted in the dried cake itself and in the freeze-drying process. The cakes were subject to shrinkage in size (from the original volume of the frozen solution), discoloration, hydroscopicity, physical instability and failure to yield a clear solution on reconstitution. In the drying process, there occurred melting-back and bubbling, loss of material being entrained by the rapidly moving vapor stream and critical limits in the control of vacuum and temperature.

By means of the step of incorporating mannitol in the vehicle prior to freezing the disadvantages previously observed in the processing and cake are not encountered.

An additional advantage in freeze-drying a solution consisting essentially of mannitol is the provision of a cake which can serve as a placebo or control for use in clinical investigations. The quality of not shrinking when dried provides a cage which to outward appearance is similar to the cake of the medicament containing counterpart thereby assuring a "blind" study.

In preparing the compositions, mannitol is dissolved in pyrogen free water for injection. The concentration of mannitol in solution can be from about 1% to about 15% w/w. The solution is then sterilized, filled into a suitable container, frozen and dried under vacuum. The volume of the solution filled into the container prior to freezing and drying will determine the volume of the dried cake.

In the freeze-dried cake consisting essen-

tially of mannitol additional adjuvants can be added, for example local anesthetic, preservative, coloring agent (when preparing placebos to serve as controls), and the like known in the parenteral art. In general, such additives constitute a negligible amount, about 1% of w/w of the cake.

In preparing medicament containing compositions, the medicament is dissolved in the aqueous vehicle, either before or after the mannitol is added. In the dry cake mannitol comprises from about 5% to about 99% w/w, and the medicinal agent and adjuvants from about 1% to about 95% w/w.

This invention is applicable to a wide variety of medicinal materials, such as antibiotics, enzymes, sedatives, analgesics, hypnotics, antispasmodics, anesthetics, steroids, especially water-soluble cortical hormone derivatives, and combinations of these with each other and other medicinals. The process is applicable whenever it is desired to provide compositions of medicinal materials in the free-dried state.

The following examples are illustrative of the process of this invention but are not to be construed as limiting.

EXAMPLE 1

1,000 vials are prepared from the following types and amounts of ingredients:

Mannitol NF	50 grams
Water for Injection q.s.	1800 c.c.

The mannitol is dissolved in sufficient water to make 1,800 c.c. The solution is passed through a clarifying and sterilizing filter. 1.8 c.c. of solution is filled into each of 1,000 sterile vials, the solution frozen, and the water removed by drying. The vials are then capped.

EXAMPLE 2

130 vials are prepared from the following types and amounts of ingredients:

Propylthiouracil	26 grams
Sodium Hydroxide	5.85 grams
Mannitol	6.5 grams
10% solution sodium hydroxide q.s.	
Water for injection q.s.	520 ml.

The sodium hydroxide is dissolved in 475 ml. of water. The propylthiouracil is stirred into the solution and then the mannitol. The pH is adjusted to pH 10.2—10.4 with 10% aqueous sodium hydroxide solution and sufficient water added to make 520 ml. of solution. The solution is then filtered through a clarifying and sterilizing filter, 4 mL is filled into each of 130, 10 c.c. vials, the solution frozen, and the water removed by drying. The vials are then capped.

EXAMPLE 3

575 vials are prepared from the following types and amounts of ingredients:

Sodium Biphosphate Anhydrous	1.09 grams
Sodium Phosphate Exsiccated NF	11.9 grams
Mannitol NF	51 grams
10% Sodium Hydroxide Solution q.s.	
Water for Injection q.s.	1150 ml.

The sodium biphosphate, sodium phosphate and mannitol are dissolved in 900 ml. of water. The pH is adjusted to pH 7.5—7.7 with 10% sodium hydroxide solution if required. Additional water is added to make 1150 ml. of solution, 2 ml. of solution is filled into each of 575 vials, the solution is frozen and the water removed by drying. The vials are then capped.

EXAMPLE 4

550 vials are prepared from the following types and amounts of ingredients:

Neomycin Sulphate	38.5 grams
Polymyxin B Sulphate (7500 u./mg)	16.8 grams
Mannitol	25.1 grams
Water for Injection q.s.	660 ml.

The neomycin, polymyxin, and mannitol are triturated together and added to 620 ml. of water. The solution is stirred until all ingredients are dissolved and the sufficient water added to make 660 ml. of solution. The solution is passed through a clarifying and sterilizing filter. 1.2 ml. of solution is filled into each of 550 2 c.c. vials, the solution frozen, and the water removed by drying. The vials are then capped.

WHAT WE CLAIM IS:—

1. A solid composition for use in parenteral administration and prepared by freeze-drying a sterile solution of mannitol in pyrogen-free water.

2. A composition as claimed in claim 1 and comprising also a parenterally acceptable medicinal agent.

3. The composition of claim 2 wherein mannitol comprises an excess of 5% w/w of the freeze-dried cake.

4. The composition of claim 2 wherein mannitol comprises from about 5% to about 99% w/w of the freeze-dried cake.

5. A method of preparing a parenterally administrable medicinal product, in which a medicinal agent is incorporated in an aqueous parenterally acceptable vehicle containing dissolved mannitol, the resulting product is frozen and ice is directly removed therefrom by sublimation in vacuo.

6. The method of claim 5 wherein the material to be frozen and dried contains from about 1% to about 15% by weight of mannitol.

7. A process for the preparation of a composition as claimed in any of claims 1 to 4

substantially as herein described with reference to the Examples.

8. A composition as claimed in any of claims 1 to 4 when prepared by a process as claimed in claims 5 to 7.

For the Applicants:
GILL, JENNINGS & EVERY,
51/52 Chancery Lane,
London W.C.2.

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